Main findings	Dose response*	Adjustment for confounders and other comments
Inverse association; statistically significant trend among nonhypertensive participants, U-shaped association among hypertensive participants	Yes/No	In hypertensive men, the protective effect of physical activity was eliminated with vigorous activity
Inverse association when adjusted only for age; null association when adjusted for cholesterol, blood pressure, BMI, diabetes, etc.	No	Follow-up report to that of Yano, Reed, McGee (1984) and Donahue et al. (1988)
Inverse association; RR for CHD incidence in low fitness group was 2.2 (95% CI, 1.1–4.7) compared with high fitness	NA	Similar results seen when men with electrocardiogram evidence of heart disease were excluded
Inverse association; point estimates and significance not reported	Yes	No adjustment for confounding variables
Inverse association; point estimates and significance not reported	Yes	No adjustment for confounding variables
Inverse association; RR for myocardial infarction and sudden death in low fit group was 1.6 relative to high fit	Yes	One of two studies to simultaneously evaluate associations of activity, fitness, and CHD
Inverse association; adjusted risk estimate of 3.2-fold increased risk of CHD death for a 35 beat/min increase in heart rate for stage II of exercise test	Yes	Extensive control for confounding influences
Inverse association; adjusted risk estimate for highest heart rate response group relative to lowest was 1.20 (95% CI, 1.10–1.26)	Yes	Risk estimate attenuated substantially after adjustment for other CHD risk factors
Inverse association; relative to more fit men, least fit men had an adjusted risk of 1.46 (95% CI, 0.94–2.26)	Yes	One of two studies to simultaneously evaluate activity and fitness in relation to CHD mortality

Abbreviations: BMI = Body mass index (wt [kg] /ht [m]^2); CHD = coronary heart disease; CI = confidence interval; ICD = International Classification of Diseases (8 and 9 refer to editions); IMF = ischemic myocardial fibrosis; RR = relative risk.

*A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

lipids in children (Lee, Lauer, Clarke 1986), and that CHD risk factor patterns persist from childhood to adulthood (Webber et al. 1991; Mahoney et al. 1991).

Recently, Armstrong and Simons-Morton (1994) reviewed the research literature on physical activity and blood lipids in children and adolescents, including over 20 observational and 8 intervention studies. They concluded that the cross-sectional observational studies did not demonstrate a relationship between physical activity level or cardiorespiratory fitness and total cholesterol, LDL-C, or HDL-C, especially when differences in body weight or fat were taken into account, suggesting that activity and body fat are not independently related to serum lipids. However, highly physically active or fit children and adolescents tended to have higher HDL-C than their inactive or unfit peers. The intervention studies generally showed favorable effects of exercise on LDL-C or HDL-C only in children and adolescents who were at high risk for CHD because of obesity, insulin-dependent diabetes mellitus, or having a parent with three or more CHD risk factors.

Alpert and Wilmore (1994) recently reviewed the research literature on physical activity and blood pressure in children and adolescents, including 18 observational and 11 intervention studies. These authors found evidence in studies of normotensive children and adolescents that higher levels of physical activity tended to be related to lower blood pressure. The associations were generally reduced in magnitude in those studies that adjusted for BMI, suggesting that lower body fat mass may at least partly explain why physical activity is related to lower blood pressure. Intervention studies tended to show that training programs lowered blood pressure by 1–6 mm Hg in normotensive children and adolescents, although the effects were inconsistent for boys and girls and for systolic and diastolic blood pressure. In hypertensive children and adolescents, physical activity interventions lowered blood pressure to a greater degree than in their normotensive peers (by approximately 10 mm Hg), although statistical significance was not always achieved because of small sample sizes.

Interpreting these studies on lipids and blood pressure in children and adolescents is hindered by several factors. Studies used a variety of physical activity categorizations, and the interventions covered a wide range of frequency, type, duration, and intensity, which were not all specified. The difficulties of assessing physical activity by self-report in children and adolescents, together with the highly self-selected population in the observational studies, may account for the less consistent findings on lipids and physical activity that were reported for children and adolescents than for adults. The relationship between dose of physical activity and amount of effect on blood pressure or serum lipids in children has not been adequately addressed.

Nonetheless, there appears to be some evidence, although not strong, of a direct relationship between physical activity and HDL-C level in children and adolescents. There is also evidence that increased physical activity can favorably influence the lipid profile in children and adolescents who are at high risk of CHD. Similarly, the evidence suggests that physical activity can lower blood pressure in children and adolescents, particularly in those who have elevated blood pressure.

Stroke

A major cardiovascular problem in developed countries, stroke (ischemic stroke and hemorrhagic stroke) is the third leading cause of death in the United States (NCHS 1994). Atherosclerosis of the extracranial and intracranial arteries, which triggers thrombosis, is thought to be the underlying pathologic basis of ischemic stroke. Cigarette smoking and high blood pressure are major risk factors for ischemic stroke, whereas high blood pressure is the major determinant of hemorrhagic stroke. The studies cited in this section examined the association between reported level of physical activity and stroke. No published studies have examined the association between cardiorespiratory fitness and stroke.

Fourteen population-based studies (four that include women) relate physical activity to risk of all types of stroke; these closely parallel the study designs and populations previously cited for CVD and CHD (Table 4-3). Thirteen of the studies were cohort studies (follow-up range, 5–26 years). Only eight found an inverse association. As with the earlier studies on CHD, the earlier studies of stroke did not permit a dose-response evaluation. Among later studies that could do so by virtue of design, half did not find a gradient. This outcome, coupled with some suggestion of a "U-shaped" association

in two studies (Menotti and Seccareccia 1985; Lindsted, Tonstad, Kuzma 1991), casts doubt on the nature of the association between physical activity and risk of both types of strokes combined.

Because of their different pathophysiologies, physical activity may not affect ischemic and hemorrhagic stroke in the same way; this issue requires more research. Only one study distinguished between ischemic and hemorrhagic stroke (Abbott et al. 1994). In this study, inactive men were more likely than active men to have a hemorrhagic stroke; physical activity was also associated with a lower risk of ischemic stroke in smokers but not in nonsmokers.

Thus the existing data do not unequivocally support an association between physical activity and risk of stroke.

High Blood Pressure

High blood pressure is a major underlying cause of cardiovascular complications and mortality. Organ damage and complications related to elevated blood pressure include left ventricular hypertrophy (which can eventually lead to left ventricular dysfunction and congestive heart failure), hemorrhagic stroke, aortic aneurysms and dissections, renal failure, and retinopathy. Atherosclerotic complications of high blood pressure include CHD, ischemic stroke, and peripheral vascular disease. Although rates of hypertension have been declining in the United States since 1960, nearly one in four Americans can be classified as being hypertensive (DHHS 1995).

Prospective observational studies relating physical activity level or cardiorespiratory fitness to risk of hypertension are summarized in Table 4-4. Several cohort studies have followed male college alumni after graduation. One found later development of hypertension to be inversely related to the reported number of hours per week of participation in sports or exercise while in college (Paffenbarger, Thorne, Wing 1968). In a later follow-up of the same cohort, using information on physical activity during mid-life, vigorous sports were associated with a 19–30 percent reduction in risk of developing hypertension over the 14-year period (Paffenbarger et al. 1991). Follow-up of a different cohort of male college alumni similarly showed the least active men to have a 30 percent increased risk of developing hypertension (Paffenbarger et al. 1983). In a study of 55- through 69-year-old women followed for 2 years, the most active women were found to have a 30 percent reduced risk of developing hypertension (Folsom et al. 1990).

One randomized trial for the primary prevention of hypertension has been conducted. A 5-year trial of a nutrition and physical activity intervention showed that the incidence of hypertension for the intervention group was less than half that of the control group (Stamler et al. 1989). Participants in the intervention group lost more weight than those in the control group, reduced more of their sodium and alcohol intake, and were more likely to become more physically active. Although the effects of the nutritional and physical activity components of this intervention cannot be separated, the study does show that the risk for developing hypertension among persons who are at high risk for the disease can be lowered by weight loss and improvements in dietary and physical activity practices.

Like physical inactivity, low cardiorespiratory fitness in middle age is associated with increased risk for high blood pressure. After adjustment for sex, age, baseline blood pressure, and body mass index, persons with low cardiorespiratory fitness had a 52 percent higher risk of later developing high blood pressure than their fit peers (Blair et al. 1984).

Taken together, the cohort studies show that physical inactivity is associated with an increased risk of later developing hypertension among both men and women. Three of the studies had more than two categories of physical activity for comparison, and each demonstrated a dose-response gradient between amount of activity and degree of protection from hypertension. Point estimates for quantification of risk suggest that those least physically active have a 30 percent greater risk of developing hypertension than their most active counterparts. Unfortunately, none of these studies was conducted in minority populations, which have a disproportionate burden of hypertensive disease (DHHS 1995).

Several randomized controlled trials have been conducted to determine the effects of exercise on blood pressure in people with elevated blood pressure levels. The reduction of elevated blood pressure is important for preventing stroke and CHD, for which high blood pressure is a risk factor with a dose-response relationship (NIH 1992). Thirteen

Table 4-3. Population-based studies of association of physical activity with stroke (CVA)

Study	Population	Definition of physical activity	Definition of stroke
Paffenbarger and Williams (1967)	> 50,000 US male college alumni aged 30–70years	Participation in college varsity athletics (yes/no)	Hemorrhagic and ischemic stroke death (n = 171)
Paffenbarger (1972)	3,991 US longshoremen aged 35 years and older; 18.5-year follow-up from 1951	Occupational activity (cargo handler or not)	Hemorrhagic and ischemic stroke death (n = 132)
Kannel and Sorlie (1979)	1,909 Framingham (MA) men aged 35–64 at 4th biennial examination; 14-year follow-up	Physical activity index based on hours per day spent at activity-specific intensity	Cerebrovascular accident (n = 87)
Salonen et al. (1982)	3,829 women and 4,110 men aged 30–59 years from Eastern Finland; 7-year follow-up	Dichotomous assessment of occupational physical activity (low/high)	Cerebral stroke (ICD-8 430–437) morbidity and mortality among men (n = 71) and women (n = 56)
Herman et al. (1983)	132 hospitalized Dutch stroke case-patients and 239 age- and sex-matched controls; men and women aged 40–74 years	Leisure-time physical activity (greatest portion of one's lifetime) ranging from little to regular-heavy	Rapidly developed clinical signs of focal or global disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than vascular origin
Paffenbarger et al. (1984)	16,936 US male college alumni who entered college between 1916 and 1950; followed from 1962–1978	Physical activity index estimated from reports of stairs climbed, city blocks walked, and sports played each week	Death due to stroke (n = 103)
Menotti and Seccareccia (1985)	99,029 Italian males railroad employees aged 40–59 years; 5-year follow-up	Classification of occupational physical activity (heavy, moderate, sedentary)	Fatal stroke (n = 187)
Lapidus and Bengtsson (1986)	1,462 Swedish women aged 38–60; follow-up between 1968 and 1981	Work and leisure physical activity assessed via 4-scales for lifetime and for the time before 1968 baseline	Fatal and nonfatal stroke (n = 13)
Menotti et al. (1990)	8,287 men aged 40–59 years in six of seven countries from Seven Countries Study; 20-year follow-up	Classification of occupational physical activity (heavy, moderate, sedentary)	Fatal stroke (cohort analysis)

Main findings	Dose response*	Adjustment for confounders and other comments
Inverse association; nondecedents were 2.2 times as likely to have participated in varsity sports than were decedents; hemorrhagic strokes = 2.1, occlusive strokes = 2.5	NA	Results adjusted for age only
Noncargo handlers were 1.11 times as likely as cargo handlers to die from stroke	NA	Results adjusted for age only
Inverse association between physical activity index and 14-year incidence of stroke	Yes	No statistical significance after controlling for several confounding variables
Inverse association with statistically significant RRs for men and women with low levels of physical activity at work were 1.5 (95% CI, 1.2–2.0) for men and 2.4 (95% CI, 1.5–3.7) for women	NA	Evidence for inverse association for low activity during leisure time, but no statistical significance after adjustment for other factors
Inverse association; relative to lowest physical activity category, risk estimates were 0.72 (95% CI, 0.37–1.42) for moderate and 0.41 (95% CI, 0.21–0.84) for high categories	Yes	Adjusted for a variety of potential confounding influences
Inverse association; relative to highest category of index (2,000+ kcal/week), risk estimates in next two lower categories were 1.25 and 2.71, respectively	Yes	Significant dose-response trend after adjusting for differences in age, cigarette smoking, and hypertension prevalence
Nonlinear "U" shape association; relative to sedentary category, men in moderate and heavy occupational activity categories had risks of 0.65 and 1.0, respectively	No	Age-adjusted only
Inverse association; women with low physical activity at work were 7.8 times as likely as others to have stroke (95% CI, 2.7–23.0); womenwith low physical activity leisure were 10.1 times as likely as others to have stroke (95% CI, 3.8–27.1)	NA	Age-adjusted only
Null association	No	No association after statistical adjustment for risk factors

Table 4-3. *Continued*

Study	Population	Definition of physical activity	Definition of stroke
Harmsen et al. (1990)	7,495 Swedish men aged 47–55 years at baseline examination; 11.8-year average follow-up	Physical activity at work and leisure hours (low, high)	Fatal stroke (all and subtypes) (n = 230)
Lindsted, Tonstad, Kuzma, (1991)	9,484 male Seventh-Day Adventists aged ≥ 30 years; 26-year follow-up	Self-report of physical activity level in 1960 (highly active, moderately active, low activity)	Fatal stroke (n = 410)
Wannamethee and Shaper (1992)	7,735 British men aged 40–59 years; 8.5-year follow-up	Self-report of physical activity at baseline; 6-point scale defined on the basis of type and frequency of activity	Fatal and nonfatal stroke (n = 128)
Abbott et al. (1994)	7,530 Hawaiian men of Japanese ancestry aged 45–68 years; 22-year follow-up	Self-report of 24-hour habitual physical activity in 1965–1968 (inactive, partially active, active)	Fatal and nonfatal neurologic deficit with sudden occurrence and remaining present for at least 2 weeks or until death (subtypes) (n = 537)
Kiely et al. (1994)	Four cohorts of Framingham (MA) men and women: cohort I—1,897 men aged 35–69 years; cohort II—2,299 women aged 35–68 years; cohort III—men aged 49–83 years; cohort IV—women aged 49–83 years; follow-up for cohorts I and II up to 32 years, for cohorts III and IV up to 18 years	Self-report of daily activity level; composite score formulated from index and categorized into high, medium, and low physical activity	Fatal and nonfatal first occurrence of atherothrombotic brain infarction, cerebral embolism, or other stroke (cohort I, n = 195; cohort II, n = 232; cohort III, n = 113; cohort IV, n = 140)

Main findings	Dose response*	Adjustment for confounders and other comments
Null association; relative to low physical activity category, slightly elevated estimates were observed for all strokes and subtypes for high activity group	No	No association after statistical adjustment for risk factors
Nonlinear "U" shape association; relative to low activity level, risk estimates were 0.78 (95% CI, 0.61–1.00) for moderate activity and 1.08 (95% CI, 0.58–2.01) for high activity	No	Adjusted for sociodemographic factors, BMI, and dietary pattern
Inverse association; statistically significant linear trend of lower risk of stroke with higher physical activity scale	Yes	Linear trend observed in men both with and without existing ischemic heart disease
Null association seen for all strokes and all subtypes for men aged 45–54 years	Yes, in older	No association of physical activity to risk of stroke in older smokers
Inverse association seen for all strokes and subtypes for men aged 55–68 years	No in younger	
Risk estimate relative to low physical activity group:		Control for many confounding factors; nonlinear association in women only (cohorts III and IV); suggestion of threshold relationship (cohort III)
cohort I—nonsignificant inverse association for medium group = 0.90 (0.62–1.31)	Yes, C I	
and for high group = 0.84 (0.59–1.18);	Yes, C I	
cohort II—nonsignificant nonlinear association for medium group = 1.21 (0.89–1.63)	No, C II	
and for high group = 0.89 (0.60–1.31);	No, C II	
cohort III—significant inverse association for medium group = 0.41 (0.24–0.69)	Yes, C III	
and for high group = 0.53 (0.34–0.84);		
cohort IV—nonsignificant nonlinear association for medium group = 0.97 (0.64–1.47)	No, C IV	
and for high group = 1.21		

Abbreviations: BMI = body mass index (wt [kg] /ht [m]^2); CVA = cerebrovascular accident; CI = confidence interval; ICD = International Classification of Diseases (8 and 9 refer to editions); RR = relative risk.

*A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

Table 4-4. Population-based cohort studies of association of physical activity with hypertension

Study	Population	Definition of physical activity	Definition of hypertension
Paffenbarger, Thorne, Wing (1968)	7,685 men who attended the University of Pennsylvania between 1931 and 1940 and who responded to a questionnaire in 1962	Reported hours per week of participation in sports or exercise in college	Self-reported incidence of physician-diagnosed hypertension from mail-back health questionnaire (n = 671)
Paffenbarger et al. (1983)	14,998 US male college alumni who entered college between 1916 and 1950; followed from 1962–1972 (for 6–10 years)	Physical activity index (kcal/week) estimated from reports of stairs climbed, city blocks walked, and sports played each week, assessed by mail-back questionnaire in 1962 or 1966	Self-reported incidence of physician-diagnosed hypertension from mail-back health questionnaire (n = 681)
Blair et al. (1984)	4,820 US men and 1,219 US women patients of a preventive medical clinic aged 20–65 years at baseline	Maximal aerobic capacity estimated by exercise tests, categorized into "high" fitness (≥ 85th percentile) and "low" fitness	Self-reported incidence of physician-diagnosed hypertension (n = 240)
Stamler et al. (1989)	201 US men and women with diastolic blood pressure 85–89 mm Hg or 80–84 mm Hg (if overweight) were randomly assigned to control or nutritional/ hygienic intervention (including exercise)	Self-report of moderate physical activity	Initiation of hypertensive therapy or sustained elevation of diastolic blood pressure ≥ 90 mm Hg
Folsom et al. (1990)	41,837 Iowa women aged 55–69 years; 2-year follow-up	Self-reported frequency of leisure-time physical activity from mail-back survey	Self-reported incidence of physician-diagnosed hypertension
Paffenbarger et al. (1991)	5,463 male college alumni from the University of Pennsylvania	Self-report of physical activity from mail-back questionnaire in 1962	Self-reported incidence of physician-diagnosed hypertension from mail-back questionnaire in 1976 (n = 739)

Main findings	Dose response*	Adjustment for confounders and other comments
Inverse association; respondents who reported participation in sports or exercise fewer than 5 hours per week had a significantly increased age- and interval-adjusted risk of physician-diagnosed hypertension (RR = 1.30, $p < 0.01$)	NA	Adjustments for age and follow-up had little effect
Inverse association; alumni with < 2,000 kcal/week of energy expenditure had RR of 1.30 (95% CI, 1.09–1.55) of developing hypertension relative to others	Yes, especially in heavier men	Increased risk observed for less active alumni with stratification of student blood pressure, alumnus BMI, increase in BMI since college, and family history of hypertension
Patients in low fitness category were 1.52 times as likely (95% CI, 1.08–2.15) to develop hypertension as those in high fitness category	NA	Extensive control for confounding variables; no sex-specific analyses
Control group RR = 2.4 (90% CI, 1.2–4.8) of developing hypertension when compared with the intervention group	NA	Intervention was combined nutritional, weight loss, and physical activity
Inverse association; relative to women at low levels of physical activity, women at high and moderate levels had 30% and 10% lower age-adjusted risks of developing hypertension (RR high = 0.70, 95% CI, 0.6–0.9; RR moderate = 0.90, 95% CI, 0.7–1.1)	Yes	Adjustment for BMI, waist-to-hip ratio, cigarette smoking, and age eliminated the association with physical activity
Vigorous sports play in 1962 was associated with a 30% reduced risk of developing hypertension	Yes	Adjusted for age, BMI, weight gain since college, and parental history of hypertension

Abbreviations: BMI = body mass index (wt [kg] /ht [m]^2); CI = confidence interval; RR = relative risk.

*A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

controlled trials of habitual activity and blood pressure were analyzed in a meta-analysis by Arroll and Beaglehole (1992), and nine randomized controlled trials of aerobic exercise using the lower extremities (e.g., walking, jogging, cycling) and blood pressure were analyzed in a meta-analysis by Kelley and McClellan (1994). The two meta-analyses independently concluded that aerobic exercise decreases both systolic and diastolic blood pressure by approximately 6–7 mm Hg. Some of the studies were conducted with persons with defined hypertension (> 140/90 mm Hg), and others were conducted with persons with high normal blood pressure. Most of the studies tested aerobic training of 60–70 percent maximum oxygen uptake, 3–4 times/week, 30–60 minutes per session.

Three trials have specifically examined the effect of different intensities of exercise on blood pressure. Hagberg et al. (1989) randomly assigned 33 hypertensive participants to a nonexercising control group and to two groups participating in different intensities of exercise (53 percent and 73 percent of $\dot{V}O_2$ max) for 9 months. Both exercise groups had comparable decreases in diastolic blood pressure (11–12 mm Hg), and the lower-intensity group had a greater decrease in systolic blood pressure than the higher-intensity group (20 mm Hg vs. 8 mm Hg). All the decreases were statistically significant when compared with the control group's blood pressure level, except the 8 mm Hg decrease in systolic blood pressure in the higher-intensity group. Matsusaki and colleagues (1992) randomly assigned 26 mildly hypertensive participants to two exercise intensities (50 percent $\dot{V}O_2$max and 75 percent $\dot{V}O_2$max) for 10 weeks. The pretest-to-posttest decreases in systolic and diastolic blood pressure in the lower-workload group were significant (9 mm Hg/6 mm Hg), but those in the higher-intensity group were not (3 mm Hg/5 mm Hg). Marceau and colleagues (1993) used a randomized crossover design to compare intensities of 50 percent and 70 percent $\dot{V}O_2$max training on 24-hour ambulatory blood pressure in persons with hypertension. A similar reduction in 24-hour blood pressure was observed for both training intensities (5 mm Hg decrease), but diurnal patterns of reduction were different.

These trials provide some evidence that moderate-intensity activity may achieve a similar, or an even greater, blood-pressure-lowering effect than vigorous-intensity activity. Because few studies have directly addressed the intensity question, however, the research base is not strong enough to draw a firm conclusion about the role of activity intensity in lowering blood pressure. It is not clear, for example, how the findings could have been affected by several issues, such as use of antihypertensive medications, changes in body weight, lack of direct intervention-control comparisons, dropout rates, and total caloric expenditure.

Biologic Plausibility

Multiple physiological mechanisms may contribute to the protective effects of physical activity against CVDs. Postulated mechanisms involve advantageous effects on atherosclerosis, plasma lipid/lipoprotein profile, blood pressure, availability of oxygenated blood for heart muscle needs (ischemia), blood clotting (thrombosis), and heart rhythm disturbances (arrhythmias) (Haskell 1995; Leon 1991a; Gordon and Scott 1991).

Other effects of activity that may be associated with modifications of CVD risk include reduced incidence of obesity, healthier distribution of body fat, and reduced incidence of non–insulin-dependent diabetes. These other effects are discussed in later sections of this chapter.

Atherosclerosis

Atherosclerosis begins when cholesterol is transported from the blood into the artery wall by lipoproteins, particularly LDL (Getz 1990; Yanowitz 1992). The formation of atherosclerotic plaques is increased at sites where the blood vessel lining is injured, which may occur in areas where blood flow is uneven (e.g., near the origin or branching of major vessels). An inflammatory reaction leads to the formation of atherosclerotic plaques in the wall of the artery.

In animal studies, exercise has been seen to protect against the effects of excess cholesterol and other contributors to the development of atherosclerosis (Kramsch et al. 1981). In addition, longitudinal studies of men with coronary artery disease have shown that endurance training, together with a cholesterol-lowering diet and interventions for other CVD risk factors, can help prevent the progression or reduce the severity of atherosclerosis in the coronary

arteries (Ornish et al. 1990; Schuler et al. 1992; Hambrecht et al. 1993; Haskell et al. 1994). There is also an inverse relationship between cardiorespiratory fitness and ultrasound-measured severity of atherosclerosis in neck arteries to the head (carotid arteries) (Rauramaa et al. 1995).

Plasma Lipid/Lipoprotein Profile

The relationships of physical activity to blood lipid and lipoprotein levels in men and women have been reviewed extensively (Leon 1991a; Krummel et al. 1993; Superko 1991; Durstine and Haskell 1994; Stefanick and Wood 1994). Of more than 60 studies of men and women, about half found that exercise training is associated with an increase in HDL. HDL, a lipid scavenger, helps protect against atherosclerosis by transporting cholesterol to the liver for elimination in the bile (Tall 1990). Cross-sectional studies show a dose-response relationship between the amount of regular physical activity and plasma levels of HDL (Leon 1991c). In these studies, the HDL levels of endurance-trained male and female athletes were generally 20 to 30 percent higher than those of healthy, age-matched, sedentary persons.

Moderate-intensity exercise training appears to be less likely to increase HDL levels in young to middle-aged women than men in the same age range (Leon 1991a; Kummel et al. 1993; Durstine and Haskell 1994). Moderate-intensity exercise was seen to increase HDL as much as more vigorous exercise in one randomized controlled trial of women (Duncan, Gordon, Scott 1991).

Studies have found that even a single episode of physical activity can result in an improved blood lipid profile that persists for several days (Tsopanakis et al. 1989; Durstine and Haskell 1994). Evidence also shows that exercise training increases lipoprotein lipase activity, an enzyme that removes cholesterol and fatty acids from the blood (Stefanick and Wood 1994). Exercise training also reduces elevated levels of triglycerides (Leon 1991c; Durstine and Haskell 1994), another blood lipid associated with heart disease.

Blood Pressure

The mechanisms by which physical activity lowers blood pressure are complicated (Leon 1991a; American College of Sports Medicine [ACSM] 1993; Fagard et al. 1990) and are mentioned only briefly here (see also Chapter 3). Blood pressure is directly proportional to cardiac output and total resistance in the peripheral blood vessels. An episode of physical activity has the immediate and temporary effect of lowering blood pressure through dilating the peripheral blood vessels, and exercise training has the ongoing effect of lowering blood pressure by attenuating sympathetic nervous system activity (Leon 1991a; ACSM 1993; Fagard et al. 1990). The reduced sympathetic activity may reduce renin-angiotensin system activity, reset baroreceptors, and promote arterial vasodilatation—all of which help control blood pressure. Improved insulin sensitivity and the associated reduction in circulating insulin levels may also contribute to blood pressure reduction by decreasing insulin-mediated sodium reabsorption by the kidney (Tipton 1984).

Ischemia

Clinical symptoms of atherosclerotic CHD occur when the heart muscle (myocardium) needs more oxygen than can be supplied from blood flowing through narrowed coronary arteries. This oxygen shortage leads to ischemia in the heart muscle—that is, to inadequate oxygenated blood for myocardial demand. Adaptations to a gradual reduction in blood flow may reduce the likelihood of myocardial ischemia. For example, new blood vessels may develop from other coronary arteries to provide an auxiliary blood supply (Cohen 1985). A person with advanced atherosclerotic CHD may remain free of symptoms at rest but may develop ischemic chest pain (angina pectoris) or electrocardiographic changes during physical exertion, which generally result from too high a myocardial oxygen demand for the blood supply available through partially occluded coronary arteries and collateral vessels (Smith and Leon 1992). Less commonly, angina pectoris may result from transient constriction (spasm) of a large coronary artery, generally at the site of an atherosclerotic plaque, or from spasm of small arterial vessels that have no evidence of plaque formation.

A recent review has summarized adaptations in the coronary circulation that are induced by endurance exercise training and that can decrease the likelihood of ischemia (Laughlin 1994). Data obtained primarily from research on animals have

demonstrated that exercise leads to a greater capacity to increase coronary blood flow and an improved efficiency of oxygen exchange between blood in the capillaries and the heart muscle cells. These functional changes are the result of a remodeled vascular structure, improved control of blood flow dynamics, and promotion of biochemical pathways for oxygen transfer.

The first and most consistent structural adaptation to exercise is an increase in the interior diameter of the major coronary arteries and an associated increase in maximal coronary blood flow (Leon and Bloor 1968, 1976; Scheuer 1982; Laughlin 1994). The second vascular adaptation is the formation of new myocardial blood vessels (capillaries and coronary arterioles) (Tomanek 1994; Leon and Bloor 1968). Animal studies also have shown that exercise training alters coronary vascular reactivity and thereby improves control of blood flow and distribution (Overholser, Laughlin, Bhatte 1994; Underwood, Laughlin, Sturek 1994). This adaptation may reduce the incidence of spasms in the proximal coronary arteries and arterioles (Laughlin 1994). In addition, exercise training results in a reduced workload on the heart due to both an increase in compliance of the heart and a relative reduction in peripheral resistance; together, these reduce myocardial oxygen demand (Jorgensen et al. 1977).

Thrombosis

An acute coronary event is usually initiated by disruption of an atherosclerotic plaque within an artery (Smith and Leon 1992). Platelet accumulation at the injury site initiates a cascade of processes leading to clot formation (thrombosis), which further reduces or completely obstructs coronary flow. A major obstruction of flow in a coronary artery may lead to the death of heart muscle (myocardial infarction) in the area served by that artery. These obstructions can, in addition, trigger potentially lethal disturbances in the rhythm of the heart (cardiac arrhythmia).

Thrombosis, usually occurring at the site of rupture or fissuring of an atherosclerotic plaque, is the precipitating event in the transition of silent or stable coronary artery disease to acute ischemic events, such as unstable angina, acute myocardial infarction, or sudden cardiac death, and in the occurrence of ischemic stroke (Davies and Thomas 1985; Falk 1985). Endurance training reduces thrombosis by enhancing the enzymatic breakdown of blood clots (fibrinolysis) and by decreasing platelet adhesiveness and aggregation (which helps prevent clot formation) (Kramsch et al. 1981; Leon 1991b).

Arrhythmia

Although persons with coronary artery disease have an increased risk of ventricular fibrillation (a life-threatening heart rhythm disturbance) during acute physical activity, persons with a healthy cardiovascular system do not incur this elevated risk (Siscovick et al. 1984; Mittleman et al. 1993; Willich et al. 1993; Thompson and Mitchell 1984; Thompson, Funk, et al. 1982; Haskell 1995; Dawson, Leon, Taylor 1979). Exercise training may reduce the risk of ventricular fibrillation in healthy persons and in cardiac patients by improving myocardial oxygen supply and demand and by reducing sympathetic nervous system activity (Leon 1991c). Evidence from epidemiologic studies shows that a physically active lifestyle reduces the risk of sudden cardiac death (Leon et al. 1987). A meta-analysis of studies that examined use of physical activity for cardiac rehabilitation showed that endurance exercise training reduced the overall risk of sudden cardiac death even among persons with advanced coronary atherosclerosis (O'Connor et al. 1989).

Conclusions

The epidemiologic literature supports an inverse association and a dose-response gradient between physical activity level or cardiorespiratory fitness and both CVD in general and CHD in particular. A smaller body of research supports similar findings for hypertension. The biological mechanisms for these effects are plausible and supported by a wealth of clinical and observational studies. It is unclear whether physical activity plays a protective role against stroke.

Cancer

Cancer, the second leading cause of death in the United States, accounts for about 25 percent of all deaths, and this percentage is increasing (NCHS 1996; American Cancer Society [ACS] 1996). The ACS has estimated that 1,359,150 new cases of

cancer and 554,740 cancer-related deaths will occur among Americans during 1996 (ACS 1996). Physical inactivity has been examined as an etiologic factor for some cancers.

Colorectal Cancer

Colorectal cancer has been the most thoroughly investigated cancer in epidemiologic studies of physical activity. To date, nearly 30 published studies have examined the association between physical activity and risk of developing colon cancer alone.

Studies that combined colon and rectal cancers as a single endpoint—colorectal cancer—are only briefly reviewed here because current research, summarized in this section, suggests that the relationship between physical activity and risk of colon cancer may be different from that for rectal cancer. Among nine studies that have examined the relationship between physical activity and colorectal cancer, one reported an inverse relationship (Wu et al. 1987), and three reported positive associations that were not statistically significant (Garfinkel and Stellman 1988; Paffenbarger, Hyde, Wing 1987 [for analysis of two cohorts]). One (Kune, Kune, Watson 1990) reported no significant associations, and in the four other studies (Albanes, Blair, Taylor 1989; Ballard-Barbash et al. 1990; Markowitz et al. 1992; Peters et al. 1989), the associations lacked consistency in subpopulations within the study, anatomic subsites of the large bowel, or measures of physical activity. Colorectal adenomas are generally thought to be precursors to colorectal cancers. A single study of colorectal adenomatous polyps has reported an inverse relationship between risk of adenomas and level of total physical activity (Sandler, Pritchard, Bangdiwala 1995). Another study of colorectal adenomas also found an inverse association, but only for running or bicycling, and only with one of two different comparison groups (Little et al. 1993).

Colon Cancer

Of the 29 studies of colon cancer, 18 used job title as the only measure of physical activity and thus addressed only occupational physical activity. These studies are a mix of mortality and incidence studies, and few have evaluated possible confounding by socioeconomic status, diet, and other possible risk factors for colon cancer. Nonetheless, findings from these 18 studies have been remarkably consistent: 14 studies (Brownson et al. 1989; Brownson et al. 1991; Chow et al. 1993; Dosemeci et al. 1993; Fraser and Pearce 1993; Fredriksson, Bengtsson, Hardell 1989; Garabrant et al. 1984; Gerhardsson et al. 1986; Kato, Tominaga, Ikari 1990; Lynge and Thygesen 1988; Marti and Minder 1989; Peters et al. 1989; Vena et al. 1985; Vena et al. 1987) reported a statistically significant inverse relationship between estimated occupational physical activity and risk of colon cancer. Four studies (Arbman et al. 1993; Vetter et al. 1992; Vlajinac, Jarebinski, Adanja 1987; Vineis, Ciccone, Magnino 1993) found no significant relationship between occupational physical activity and risk of colon cancer. The 18 studies were conducted in a variety of study populations in China, Denmark, Japan, New Zealand, Sweden, Switzerland, Turkey, and the United States.

Eleven studies assessed the association between leisure-time or total physical activity and colon cancer risk in 13 different study populations (Table 4-5). These studies either measured physical activity and tracked participants over time to ascertain colon cancer outcomes or compared recalled histories of physical activity among colon cancer patients with those among controls. In eight study populations, an inverse association was reported between physical activity and risk of colon cancer, and results were generally consistent for men and women. The three studies that examined the effect of physical activity during early adulthood (Polednak 1976; Paffenbarger, Hyde, Wing 1987; Marcus, Newcomb, Storer 1994) found no effect, which could indicate that the earlier activity did not affect risk of colon cancer later in life. In studies that used more than two categories of physical activity, 10 potential dose-response relationships between level of physical activity or cardiorespiratory fitness and colon cancer risk were evaluated. Five of these showed a statistically significant inverse dose-response gradient, one showed an inverse dose-response gradient that was not statistically significant, three showed no gradient, and one showed a positive relationship that was not statistically significant.

Two studies of colon adenomas (Giovannucci et al. 1995; Kono et al. 1991) reported an inverse relationship between leisure-time physical activity and risk of colon adenomas.

Table 4-5. Epidemiologic studies of leisure-time or leisure-time plus occupational physical activity* and colon cancer

Study	Population	Definition of physical activity	Definition of cancer
Polednak (1976)	Cohort of 8,393 former US college men	College athletic status; major, minor, and nonathlete	Colon cancer mortality (n = 107)
Paffenbarger, Hyde, Wing (1987)	Cohort of 51,977 male, 4,706 female former US college students	Sports play in college	Colon cancer incidence (n = 201)
	Cohort of 16,936 male US college alumni aged 35–74 years	Physical activity index (kcal/week)	Colon cancer mortality (n = 44)
Gerhardsson, Floderus, Norell (1988)	Cohort of 16,477 Swedish men and women twins aged 43–82 years	Categories of occupational and leisure-time activity	Colon cancer incidence
Slattery et al. (1988)	Cohort of Utah men (110 cases and 180 controls) and women (119 cases and 204 controls) aged 40–79 years	Occupational and leisure-time activity were both assessed by total energy expended	Colon cancer incidence
Severson et al. (1989)	Cohort of 7,925 Japanese men aged 46–65 years	Physical activity index from Framingham study and heart rate	Colon cancer incidence (n = 172)
Gerhardsson et al. (1990)	Swedish men (163 cases) and women (189 cases) and 512 controls; all ages	Categories of occupational and leisure-time activity	Colon cancer incidence
Whittemore et al. (1990)	North American Chinese men (179 cases and 698 controls) and women (114 cases and 494 controls) aged ≥ 20 years	Time per day spent sleeping/ reclining, sitting, in light or moderate activity, and in vigorous activity	Colon cancer incidence
	Asian Chinese men (95 cases and 678 controls) and women (78 cases and 618 controls) aged 20–79 years	Time per day spent sleeping/ reclining, sitting, in light or moderate activity, and in vigorous activity	Colon cancer incidence
Lee, Paffenbarger, Hsieh (1991)	Cohort of 7,148 male male US college alumni aged 30–79 years	Index of energy expenditure based on stair climbing, walking, and sports/recreation, assessed 2 times > 11 years apart	Colon cancer incidence

Main findings	Dose response†	Adjustment for confounders and other comments
No differences in mortality	No	None
Sports play ≥ 5 hrs/week relative to < 5 hrs/week: RR = 0.91; p = 0.60	NA	Adjusted for age (2 levels of activity)
Risk increased with physical activity index: p for trend = 0.45	No	Adjusted for age, BMI, and smoking
Least active relative to most active for work and leisure: RR = 3.6 (95% CI, 1.3–9.8)	NA	Adjusted for age and sex (2 levels of activity); adjustments for possible confounders said to not change results
High activity quartile relative to low activity quartile; men: OR total 0.70 (90% CI, 0.38–1.29); women: OR total 0.48 (90% CI, 0.27–0.87)	Yes	Adjusted for age, BMI, dietary fiber, and total energyintake; greater effect with intense activity; population-based
High activity tertile relative to low activity tertile: RR 0.71 (95% CI, 0.51–0.99); high heart rate relative to low: RR 1.37 (95% CI, 0.97–1.93)	No Yes	Adjusted for age, BMI
Low activity relative to high: work and leisure, RR = 1.8 (95% CI, 1.0–3.4)	Yes	Adjusted for age, sex, BMI, dietary intake of total energy, protein, fat, fiber, and browned meat surface; population-based
Sedentary relative to active: RR = 1.6 (95% CI, 1.1–2.4) for men, RR = 2.0(95% CI, 1.2–3.3) for women	NA	Adjusted for age (2 levels of activity); population-based; adjustment for diet had little effect on findings
Sedentary relative to active: RR = 0.85 (95% CI, 0.39–1.9) for men, RR = 2.5 (95% CI, 1.0–6.3) for women	NA	Adjusted for age (2 levels of activity); population-based; no effect of physical activity after adjustment for diet
Highly active relative to inactive: RR = 0.85 (90% CI, 0.6–1.1); high lifetime activity: RR = 0.5 (90% CI, 0.3–0.9)	No	Adjusted for age

Table 4-5. *Continued*

Study	Population	Definition of physical activity	Definition of cancer
Marcus, Newcomb, Storer (1994)	Wisconsin women aged up to 74 years, 536 cases and 2,315 controls	Total strenuous physical activity during ages 14–22 years	Colon cancer incidence
Giovannucci et al. (1995)	47,723 US male health professionals aged 40–75 years	Weekly recreational physical activity index based on 8 categories of moderate and vigorous activities	Colon cancer incidence (n = 201)
Longnecker et al. (1995)	US men aged > 30 years, 163 cases 703 controls	Leisure-time vigorous physical activity	Right-sided colon cancer incidence

Dietary factors may confound or modify the association between physical activity and colon cancer risk (Willett et al. 1990). Five of the studies in Table 4-5 controlled for dietary components in analyses and continued to observe a significant inverse association (Gerhardsson, Floderus, Norell 1988; Slattery et al. 1988; Gerhardsson et al. 1990; Giovannucci et al. 1995; Longnecker et al. 1995), and in one study (Whittemore et al.1990), adjustment for dietary intakes altered findings in one study population but not in the other.

Together, the research on occupational and leisure-time or total physical activity strongly suggests that physical activity has a protective effect against the risk of developing colon cancer.

Rectal Cancer

Many of the studies on physical activity and colon cancer risk also studied rectal cancer as a separate outcome. Of 13 studies that investigated occupational physical activity alone, 10 reported no statistically significant association with rectal cancer risk (Garabrant et al. 1984; Vena et al. 1985, 1987; Gerhardsson et al. 1986; Jarebinski, Adanja, Vlajinac 1988; Lynge and Thygesen 1988; Brownson et al. 1991; Marti and Minder 1989; Peters et al. 1989; Dosemeci et al. 1993), two reported significant inverse associations (Kato, Tominaga, Ikari 1990; Fraser and Pearce 1993), and one reported a significant direct association (i.e., increasing risk with increasing physical activity) (Arbman et al. 1993).

Six of the studies that investigated the association between leisure-time or total physical activity and the risk of developing rectal cancer failed to find a significant association (Gerhardsson, Floderus, Norell 1988; Severson et al. 1989; Gerhardsson et al. 1990; Kune, Kune, Watson 1990; Lee, Paffenbarger, Hsieh 1991; Longnecker et al. 1995). In another study, Whittemore and colleagues (1990) observed a statistically significant inverse association in one study population and no effect in the other. Paffenbarger, Hyde, and Wing (1987) found an inverse relationship in one cohort and a direct relationship in the other.

Taken together, study results on both occupational and leisure-time or total physical activity suggest that risk of rectal cancer is unrelated to physical activity.

Hormone-Dependent Cancers in Women

Of the epidemiologic studies examining the relationship between physical activity and hormone-dependent cancers in women, 13 have investigated the risk associated with breast cancer, two with ovarian cancer, four with uterine corpus cancer (mostly endometrial), and one with a combination of cancers. It should be noted that studies of physical activity in women have been especially prone to misclassification problems because they did not

Main findings	Dose response†	Adjustment for confounders and other comments
Any strenuous activity relative to none: RR = 1.0 (95% CI, 0.8–1.3)	No	Adjusted for age, family history, screening sigmoidoscopy, BMI; population based
Most active quintile compared with least active quintile, RR = 0.53 (95% CI, 0.32–0.88) p for trend = 0.03	Yes	Adjusted for age, BMI, parental history of colorectal cancer, history of endoscopic screening or polyp diagnosis, smoking, aspirin use, and diet
Vigorous activity ≥ 2 hours/week relative to none: RR = 0.6 (95% CI, 0.4–1.0)	Yes	Adjusted for BMI, family history, income, race, smoking, and intakes of alcohol, energy, fat, fiber, and calcium

Abbreviations: BMI = body mass index (wt [kg] /ht [m]^2); CI = confidence interval; OR = odds ratio; RR = relative risk.

*Excludes studies where only occupational physical activity was measured.

†A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

include household work and child care in their assessment. Studies of leisure-time or total physical activity and hormone-dependent cancers in women are summarized in Table 4-6.

Breast Cancer

Four of the 13 breast cancer studies considered only occupational physical activity. Two of those studies described significant inverse associations (Vena et al. 1987; Zheng et al. 1993), and two others reported no significant association (Dosemeci et al. 1993; Pukkala et al. 1993). Only two (Dosemeci et al. 1993; Pukkala et al. 1993) adjusted for socioeconomic status, and none gathered information about reproductive factors and thus could not control for those potential confounding variables.

The epidemiologic studies of leisure-time or total physical activity and breast cancer risk have yielded inconsistent results (Table 4-6). Of these 10 studies, two reported a significant inverse association (Bernstein et al. 1994; Mittendorf et al. 1995), three reported an inverse association that was not statistically significant (Frisch et al. 1985,1987; Friedenreich and Rohan 1995), three reported no relationship (Paffenbarger, Hyde, Wing 1987; Albanes, Blair, Taylor 1989; Taioli, Barone, Wynder 1995). The other two reported a direct association, although in one this did not reach statistical significance (Dorgan et al. 1994), and in the other it remained statistically significant (after adjustment for confounding) only for physical activity at age 30–39 years (Sternfeld et al. 1993).

Even among the studies that controlled for potential confounding by reproductive factors, findings were inconsistent (Bernstein et al. 1994; Dorgan et al. 1994; Sternfeld et al. 1993; Friedenreich and Rohan 1995; Mittendorf et al. 1995; Taioli, Barone, Wynder 1995). Results were inconsistent as well among studies that included primarily postmenopausal women (i.e., all but the study by Bernstein and colleagues [1994]).

Nonetheless, it is possible that physical activity during adolescence and young adulthood may protect against later development of breast cancer. Five of the studies cited here have examined this possibility. Among these five studies, two found a strong and statistically significant reduction in risk (Bernstein et al. 1994 [RR = 0.42]; Mittendorf et al. 1995 [RR = 0.5]), one found a nonsignificant reduction in risk (Frisch et al. 1985 [RR = 0.54]), and two found a null association (Paffenbarger, Hyde, Wing 1987; Taioli, Barone, Wynder 1995). These studies thus lend limited support to the hypothesis that physical activity during adolescence

Table 4-6. Epidemiologic studies of leisure-time or leisure-time plus occupational physical activity* and hormone-dependent cancers in women

Study	Population	Definition of physical activity	Definition of cancer
Breast cancer			
Frisch et al. (1985 and 1987)	Cohort of former US college athletes and nonathletes; 5,398 women aged 21–80 years	Athletic status during college	Breast cancer prevalence (n = 69)
Paffenbarger, Hyde, Wing (1987)	Cohort of former US college students, 4,706 women	Sports play during college	Breast cancer incidence and mortality
Albanes, Blair, Taylor (1989)	NHANES cohort: 7,413 women aged 25–74 years, in US	One question on nonrecreational activity, one on recreational activity	Breast cancer incidence (n = 122)
Sternfeld et al. (1993)	254 cases and 201 controls in an HMO	Age-specific recreational activity levels	Breast cancer incidence
Bernstein et al. (1994)	Women ≥ 40 years; 545 cases and 545 controls in California, US	Participation in several leisure-time activities after menarche	Breast cancer incidence in situ and invasive
Dorgan et al. (1994)	Framingham Study cohort: 2,307 women aged 35–68 years, Massachusetts, US	Physical activity index	Breast cancer incidence (n = 117)
Friedenreich and Rohan (1995)	Australian women aged 20–74 years; 451 cases and 451 controls (matched)	Recreational physical activity index	Breast cancer incidence
Mittendorf et al. (1995)	US women aged 17–74 years; 6,888 cases and 9,539 controls	Strenuous physical activity at ages 14–22 years	Breast cancer incidence
Taioli, Barone, Wynder (1995)	All ages in US; 617 cases; 531 controls	Leisure-time physical activity at ages 15–22 years	Breast cancer incidence
Ovarian cancers			
Mink et al. (1996)	Iowa Women's Health Study; cohort of 31,396 postmenopausal women	Categories of physical activity	Ovarian cancer incidence (n = 97)

Main findings	Dose response[†]	Adjustment for confounders and other comments
Nonathletes vs. athletes: RR = 1.86 (95% CI, 1.0–3.47)	NA	Adjusted for age, family history of cancer, age at menarche, number of pregnancies, oral contraceptive use, smoking, use of estrogen, leanness
Sports play of ≥ 5 relative to < 5 hours/week RR = 0.96 (p value = 0.92)	NA	Adjusted for age
Sedentary relative to most active: RR = 1.1 (95% CI, 0.6–2.0) for nonrecreational; RR = 1.0 (95% CI, 0.6–1.6) for recreational	No	Adjusted for age; adjustment for confounders had little effect on results; suggestive of variable effects by menopausal status
For activity from age 30–39, high activity quartile vs. low activity quartile, postmenopausal OR = 2.3 (95% CI, 1.03–5.04); premenopausal OR = 2.8 (95% CI, 0.98–5.18)	Yes (opposite direction)	Adjusted for age, menopausal status, and potential confounders
≥ 3.8 hours/week relative to 0 hours of leisure-time activity, RR = 0.42 (95% CI, 0.27–0.64)	Yes	Adjusted for age, race, neighborhood, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, oral contraceptive use, lactation, family history of breast cancer, Quetelet index; population-based
High activity quartile relative to low activity quartile: RR = 1.6 (95% CI, 0.9–2.9)	Yes (opposite direction)	Adjusted for age, menopausal status, age at first pregnancy, parity, education, occupation, and alcohol
> 4,000 kcal/week in physical activity relative to none: RR = 0.73 (95% CI, 0.51–1.05)	Yes	Adjusted for BMI and energy intake; effects observed for premenopausal and postmenopausal cancer and for light and vigorous activity; population-based
≥ daily strenuous activity relative to none: RR = 0.5 (95% CI, 0.4–0.7)	Yes	Adjusted for age, parity, age at first birth, family history, BMI, prior breast disease, age at menopause, menopausal status, alcohol use, and menopausal status x BMI; population-based
> 1,750 kcal/week relative to none: RR = 1.1 (95% CI, 0.5–2.6)	No	Adjusted for age, education, BMI, age at menarche, and prior pregnancy; hospital-based
Most active relative to least active: RR = 1.97 (95% CI, 1.22–3.19)	Yes (opposite direction)	Adjusted for age, smoking, education, live births, hysterectomy, and family history

Table 4-6. *Continued*

Study	Population	Definition of physical activity	Definition of cancer
Endometrial cancers			
Levi et al. (1993)	Switzerland/Northern Italy; 274 cases and 572 controls aged 31–75	Categories of leisure-time and occupational activity	Endometrial cancer incidence
Shu et al. (1993)	Women in Shanghai, China aged 18–74 years, 268 cases and 268 controls	Occupational and nonoccupational physical activity index	Endometrial cancer incidence
Sturgeon et al. (1993)	US women aged 20–74 years; 405 cases and 297 controls	Recreational and nonrecreational activity categories	Endometrial cancer incidence
Combined set			
Frisch et al. (1985 and 1987)	Cohort of former US college athletes and nonathletes; 5,398 women aged 21–80 years	Athletic status during college	Cervix, uterus, ovary, vagina cancer prevalence (n = 37)

and young adulthood may be protective against later development of breast cancer.

Other Hormone-Dependent Cancers in Women

Too little information is available to evaluate the possible effect of physical activity on risk of ovarian cancer. Zheng and colleagues (1993) found no significant associations between occupational physical activity and risk of ovarian cancer. On the other hand, data from the Iowa Women's Health Study showed that risk of ovarian cancer among women who were most active was twice the risk among sedentary women (Mink et al. 1996).

Findings are limited for uterine corpus cancers as well. Zheng et al. (1993) found no relationship between physical activity and risk of cancer of the uterine corpus. Among the endometrial cancer studies, one (Levi et al. 1993) found a decreased risk associated with nonoccupational activity, and one (Sturgeon et al. 1993) found combined recreational and nonrecreational activity to be protective. Another study (Shu et al. 1993) found no protective effect of nonoccupational activity in any age group and a possible protective effect of occupational activity among younger women but not among older women.

In Frisch and colleagues' (1985) study of the combined prevalence of cancers of the ovary, uterus, cervix, and vagina, nonathletes were 2.5 times more likely than former college athletes to have these forms of cancer at follow-up. Because these cancers have different etiologies, however, the import of this finding is difficult to determine.

Thus the data are either too limited or too inconsistent to firmly establish relationships between physical activity and hormone-dependent cancers in women. The suggestive finding that physical activity in adolescence and early adulthood may protect against later development of breast cancer deserves further study.

Main findings	Dose response†	Adjustment for confounders and other comments
Sedentary relative to active for total activity: RR = 2.4 (95% CI, 1.0–5.8) to RR = 8.6 (95% CI, 3.0–25.3) for different ages	Yes	Adjusted for age, education, parity, menopausal status, oral contraceptive use, estrogen replacement, BMI, and caloric intake; hospital-based
Low average adult activity quartile relative to high quartile: occupational age ≤ 55 years RR = 2.5 (95% CI, 0.9–6.3), age > 55 years RR = 0.6 (no CI given); nonoccupational RR = 0.8 (95% CI, 0.5–1.3)	No	Adjusted for age, number of pregnancies, BMI, and caloric intake; possible modification of occupational activity by age; population-based
Sustained (lifetime) activity, inactive relative to active: recreational RR = 1.5 (95% CI, 0.7–3.2) nonrecreational RR = 1.6 (95% CI, 0.7–3.3)	No	Adjusted for age, study area, education, parity, oral contraceptive use, hormone replacement use, cigarette smoking, BMI, and other type of activity; recent activity also protective; population-based
Nonathletes vs. athletes: RR = 2.53 (95% CI, 1.17–5.47)	N/A	Adjusted for age, family history of cancer, age at menarche, number of pregnancies, oral contraceptive use, smoking, use of estrogen, leanness

Abbreviations: BMI = body mass index (wt [kg]/ht [m]^2); CI = confidence interval; HMO = health maintenance organization; NHANES = National Health and Examination Survey; OR = odds ratio; RR = relative risk.

*Excludes studies where only occupational physical activity was measured.

†A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

Cancers in Men

Prostate Cancer

Among epidemiologic studies of physical activity and cancer, prostate cancer is the second most commonly studied, after colorectal cancer. Results of these studies are inconsistent. Seven studies have investigated the association between occupational physical activity and prostate cancer risk or mortality. Two described significant inverse dose-response relationships (Vena et al. 1987; Brownson et al. 1991). Two showed a nonsignificant decreased risk with heavy occupational activity (Dosemeci et al. 1993; Thune and Lund 1994). In one publication that presented data from two cohorts, there was no effect in either (Paffenbarger, Hyde, Wing 1987). The remaining study (Le Marchand, Kolonel, Yoshizawa 1991) reported inconsistent findings by age: increasing risk with increasing activity among men aged 70 years or older and no relationship among men younger than age 70.

The 10 studies of leisure-time physical activity, or total physical activity, or cardiorespiratory fitness and risk of prostate cancer have also produced inconsistent results (Table 4-7). Two of the studies described significant inverse relationships (Lee, Paffenbarger, Hsieh 1992; Oliveria et al. 1996), although one of these (Lee, Paffenbarger, Hsieh 1992) observed this relationship only among men aged 70 years or older. Four studies found inverse relationships (Albanes, Blair, Taylor 1989; Severson et al. 1989; Yu, Harris, Wynder 1988; Thune and

Table 4-7. Epidemiologic studies of leisure-time or total physical activity or cardiorespiratory fitness and prostate cancer

Study	Population	Definition of physical activity or cardiorespiratory fitness	Definition of cancer
Physical activity			
Polednak (1976)	Cohort of 8,393 former US college men	College athletic status, major, minor, and nonathletes	Prostate cancer incidence (n = 124)
Paffenbarger, Hyde, Wing (1987)	Cohort of 51,977 US male former college students	Sports play	Prostate cancer incidence and mortality (n = 154)
	16,936 US male alumni aged 35–74 years	Physical activity index	Prostate cancer mortality (n = 36)
Yu, Harris, Wynder (1988)	US men, all ages, 1,162 cases and 3,124 controls	Categories of leisure-time aerobic exercise	Prostate cancer incidence
Albanes, Blair, Taylor (1989)	NHANES cohort of 5,141 US men aged 25–74 years	Categories of recreational and nonrecreational activity	Prostate cancer incidence
Severson et al. (1989)	Cohort of 7,925 Japanese men in Hawaii aged 46–65 years	Physical activity index from Framingham study and heart rate	Prostate cancer incidence
West et al. (1991)	Utah men aged 45–74 years, 358 cases and 679 controls	Categories of energy expended	Prostate cancer incidence
Lee, Paffenbarger, Hsieh (1992)	Cohort of US college alumni, 17,719 men aged 30–79 years	Physical activity index based on stair climbing, walking, playing sports	Prostate cancer incidence (n = 221)
Thune and Lund (1994)	Cohort of Norwegian 43,685 men	Recreational and occupational activity based on questionnaire; categories of occupational and leisure-time activity	Prostate cancer incidence (n = 220)
Cardiorespiratory Fitness			
Oliveria et al. (1996)	Cohort of 12,975 Texas men aged 20–80 years	Maximal exercise test	Prostate cancer incidence or mortality (n = 94)
	Cohort of 7,570 Texas men	Categories of weekly energy expenditure in leisure time	Prostate cancer incidence or mortality (n = 44)

Main findings	Dose response*	Adjustment for confounders and other comments
Major athletes relative to nonathletes, RR = 1.64 ($p < 0.05$)	No	None
Sports play ≥ 5 relative to < 5 hours/week, RR = 1.66; ($p < 0.05$)	NA	Adjusted for age (2 levels of activity)
Comparing ≥ 2,000 with < 500 kcal/week, RR = 0.57; $p = 0.33$	No	Adjusted for age, BMI, and smoking
Most sedentary relative to most active menduring leisure time, RR = 1.3 (95% CI, 1.0–1.6) for whites, RR = 1.4 (95% CI, 0.8–2.6) for blacks	Yes	Adjusted for age; in multivariate analysis, findings no longer significant for whites; hospital based
Least active relative to most active individuals, RR = 1.3 (95% CI, 0.7–2.4); for nonrecreational RR = 1.8 (95% CI, 1.0–3.3); for recreational RR = 1.8 (95% CI, 1.0–3.3)	No Yes No	Adjusted for age; further adjustment for confounders said to not affect results
Most active relative to least active men, RR = 1.05 (95% CI, 0.73–1.51); for occupation, RR = 0.77 (95% CI, 0.58–1.01); high heart rate relative to low, RR = 0.97 (95% CI, 0.69–1.36)	NA No NA	Adjusted for age, BMI
Overall no association found		For agressive tumors, physical activity was associated with increased risk, but this was not statistically significant
Men aged ≥ 70 years: comparing > 4,000 with < 1,000 kcal/week; RR = 0.53 (95% CI, 0.29–0.95); men aged < 70 years, RR = 1.21 (95% CI, 0.8–0.18)	No	Adjusted for age; no effect of activity at 2,500 kcal, the level found protective for colon cancer
Heavy occupational activity relative to sedentary, RR = 0.81 (95% CI, 0.50–1.30); regular training in leisure time relative to sedentary, RR = 0.87 (95% CI, 0.57–1.34)	No	Adjusted for age, BMI, and geographic region
Among men < 60 years, most fit relative to least fit, RR = 0.26 (95% CI, 0.10–0.63); among men > 60 years, no effect, RR not given	Yes No	Adjusted for age, BMI, and smoking Adjusted for age, BMI, and smoking
≥ 3,000 kcal/week relative to < 1,000 kcal/week, RR = 0.37 (95% CI, 0.14–0.98)	No	Adjusted for age, BMI, and smoking

Abbreviations: BMI = body mass index (wt [kg]/ht [m]^2); CI = confidence interval; RR = relative risk.

*A dose-response relationship requires more than 2 levels of comparison. In this column, "NA" means that there were only 2 levels of comparison; "No" means that there were more than 2 levels but no dose-response gradient was found; "Yes" means that there were more than 2 levels and a dose-response gradient was found.

Lund 1994), but these were not statistically significant, and one of the four (Thune and Lund 1994) showed this relationship only for those aged 60 years or older. Two studies found that men who had been athletically active in college had significantly increased risks of later developing prostate cancer (Polednak 1976; Paffenbarger, Hyde, Wing 1987). One study found no overall association between physical activity and prostate cancer risk but found a higher risk (although not statistically significant) of more aggressive prostate cancer (West et al. 1991).

The two studies of the association of cardiorespiratory fitness with prostate cancer incidence were also inconsistent. Severson and colleagues (1989) found no association between resting pulse rate and subsequent risk of prostate cancer. Oliveria and colleagues (1996) found a strong inverse dose-response relationship between fitness assessed by time on a treadmill and subsequent risk of prostate cancer.

Thus the body of research conducted to date shows no consistent relationship between prostate cancer and physical activity.

Testicular Cancer

Two studies investigated physical activity and risk of developing testicular cancer; again, results are inconsistent. A case-control study in England found that men who spent at least 15 hours per week in recreational physical activity had approximately half the risk of sedentary men, and a significant trend was reported over six categories of total time spent exercising (United Kingdom Testicular Cancer Study Group 1994). A cohort study in Norway (Thune and Lund 1994) was limited by few cases. It showed no association between leisure-time physical activity and risk of testicular cancer, but heavy manual occupational activity was associated with an approximately twofold increase in risk, although this result was not statistically significant. Thus no meaningful conclusions about a relationship between physical activity and testicular cancer can be drawn.

Other Site-Specific Cancers

Few epidemiologic studies have examined the association of physical activity with other site-specific cancers (Lee 1994). The totality of evidence provides little basis for a suggestion of a relationship.

Biologic Plausibility

Because the data presented in this section demonstrate a clear association only between physical activity and colon cancer, the biologic plausibility of this relationship is the focus of this section. The alteration of local prostaglandin synthesis may serve as a mechanism through which physical activity may confer protection against colon cancer (Shephard et al. 1991; Lee 1994; Cordain, Latin, Beanke 1986). Strenuous physical activity increases prostaglandin F_2 alpha, which strongly increases intestinal motility, and may suppress prostaglandin E_2, which reduces intestinal motility and, released in greater quantities by colon tumor cells than normal cells, accelerates the rate of colon cell proliferation (Thor et al. 1985; Tutton and Barkla 1980). It has been hypothesized that physical activity decreases gastrointestinal transit time, which in turn decreases the length of contact between the colon mucosa and potential carcinogens, cocarcinogens, or promoters contained in the fecal stream (Shephard 1993; Lee 1994). This hypothesis could partly explain why physical activity has been associated with reduced cancer risk in the colon but not in the rectum. Physical activity may shorten transit time within segments of the colon without affecting transit time in the rectum. Further, the rectum is only intermittently filled with fecal material before evacuation. Despite these hypothetical mechanisms, studies on the effects of physical activity on gastrointestinal transit time in humans have yielded inconsistent results (Shephard 1993; Lee 1994).

Conclusions

The relative consistency of findings in epidemiologic studies indicates that physical activity is associated with a reduced risk of colon cancer, and biologically plausible mechanisms underlying this association have been described. The data consistently show no association between physical activity and rectal cancer. Data regarding a relationship between physical activity and breast, endometrial, ovarian, prostate, and testicular cancers are too limited or too inconsistent to support any firm conclusions. The suggestion that physical activity in adolescence and early adulthood may protect against later development of breast cancer clearly deserves further study.

Non–Insulin-Dependent Diabetes Mellitus

An estimated 8 million Americans (about 3 percent of the U.S. population) have been diagnosed with diabetes mellitus, and it is estimated that twice that many have diabetes but do not know it (Harris 1995). More than 169,000 deaths per year are attributed to diabetes as the underlying cause, making it the seventh leading cause of mortality in the United States (NCHS 1994). This figure, however, underestimates the actual death toll: in 1993, more than twice this number of deaths occurred among persons for whom diabetes was listed as a secondary diagnosis on the death certificate. Many of these deaths were the result of complications of diabetes, particularly CVDs, including CHD, stroke, peripheral vascular disease, and congestive heart failure. Diabetes accounts for at least 10 percent of all acute hospital days and in 1992 accounted for an estimated $92 billion in direct and indirect medical costs (Rubin et al. 1993). In addition, by age 65 years, about 40 percent of the general population has impaired glucose tolerance, which increases the risk of CVD (Harris et al. 1987).

Diabetes is a heterogeneous group of metabolic disorders that have in common elevated blood glucose and associated metabolic derangements. Insulin-dependent diabetes mellitus (IDDM, or type I) is characterized by an absolute deficiency of circulating insulin caused by destruction of pancreatic beta islet cells, thought to have occurred by an autoimmune process. Non–insulin-dependent diabetes mellitus (NIDDM, or type II) is characterized either by elevated insulin levels that are ineffective in normalizing blood glucose levels because of insulin resistance (decreased sensitivity to insulin), largely in skeletal muscle, or by impaired insulin secretion. More than 90 percent of persons with diabetes have NIDDM (Krall and Beaser 1989).

Nonmodifiable biologic factors implicated in the etiology of NIDDM include a strong genetic influence and advanced age, but the development of insulin resistance, hyperinsulinemia, and glucose intolerance are related to a modifiable factor: weight gain in adults, particularly in those persons in whom fat accumulates around the waist, abdomen, and upper body and within the abdominal cavity (this is also called the android or central distribution pattern) (Harris et al. 1987).

Physical Activity and NIDDM

Considerable evidence supports a relationship between physical inactivity and NIDDM (Kriska, Blair, Pereira 1994; Zimmet 1992; King and Kriska 1992; Kriska and Bennett 1992). Early suggestions of a relationship emerged from the observation that societies that had discontinued their traditional lifestyles (which presumably included large amounts of regular physical activity) experienced major increases in the prevalence of NIDDM (West 1978). Additional evidence for the importance of lifestyle was provided by comparison studies demonstrating that groups of people who migrated to a more technologically advanced environment had higher prevalences of NIDDM than their ethnic counterparts who remained in their native land (Hara et al. 1983; Kawate et al. 1979; Ravussin et al. 1994) and that rural dwellers had a lower prevalence of diabetes than their urban counterparts (Cruz-Vidal et al. 1979; Zimmet 1981; Taylor et al. 1983; King, Taylor, Zimmet, et al. 1984).

Many cross-sectional studies have found physical inactivity to be significantly associated with NIDDM (Taylor et al. 1983; Taylor et al. 1984; King, Taylor, Zimmet, et al. 1984; Dowse et al. 1991; Ramaiya et al. 1991; Kriska, Gregg, et al. 1993; Chen and Lowenstein 1986; Frish et al. 1986; Holbrook, Barrett-Connor, Wingard 1989). Cross-sectional studies that have examined the relationship between physical activity and glucose intolerance in persons without diabetes have generally found that after a meal, glucose levels (Lindgärde and Saltin 1981; Cederholm and Wibell 1985; Wang et al. 1989; Schranz et al. 1991; Dowse et al. 1991; Kriska, LaPorte, et al. 1993) and insulin values (Lindgärde and Saltin 1981; Wang et al. 1989; McKeigue et al. 1992; Feskens, Loeber, Kromhout 1994; Regensteiner et al. 1995) were significantly higher in less active than in more active persons. However, some cross-sectional studies did not find that physical inactivity was consistently associated with NIDDM in either the entire population or in all subgroups (King, Taylor, Zimmet, et al. 1984; Dowse et al. 1991; Kriska, Gregg, et al. 1993; Montoye et al. 1977; Taylor et al. 1983; Fisch et al. 1987; Jarrett, Shipley, Hunt 1986; Levitt et al. 1993; Harris 1991). For example, the Second National Health and Nutrition Examination Survey and the Hispanic Health and Nutrition Examination Survey found that higher